NADE protein comprises the amino acid sequence as set forth in SEQ ID NO:13.

REMARKS

Claims 134-146 are pending in the subject application. By this Amendment, applicant has amended claims 134-136 and 141-143 to introduce certain format changes. Applicant has also amended the specification to introduce certain changes. Applicant has also replaced the title and the abstract in order to address certain formalities. Accordingly, claims 134-146 will still be under examination in the subject application upon entry of this Amendment.

Applicant has annexed hereto as Exhibits B, C and D, respectively, marked-up versions of the amended abstract, specification and claims.

In view of the arguments below, applicant maintains that the Examiner's objections and rejections have been overcome, and respectfully request that they be withdrawn.

Formalities

Title of the Invention

The Examiner objected to the title of the subject application as allegedly not descriptive of the invention. In response, but without conceding the correctness of the Examiner's objection, applicant notes that the title has been amended. Applicant maintains that the amended title satisfies the

requirements of 37 C.F.R. §1.72(a).

Abstract of the Disclosure

The Examiner objected to the abstract of the disclosure as allegedly lacking proper language and format. In response, but without conceding the correctness of the Examiner's objection, applicant notes that the abstract has been amended and the amended abstract is annexed as Exhibit A. Applicant maintains that the amended abstract satisfies the requirements of 37 C.F.R. §1.72(b).

Specification

The Examiner objected to the specification as allegedly unclear as to the identity of the disclosed NADE sequences. In response, but without conceding the correctness of the Examiner's objection, applicant notes that certain minor changes have been made to the specification to clarify this issue. Applicant notes that as disclosed in the specification on page 1, lines 24-32, the isolated NADE was obtained by screening a mouse cDNA library resulting in a mouse NADE nucleic acid sequence(SEQ ID NO:28) and its corresponding amino acid sequence (SEQ ID NO:12). This isolated *mouse* sequence is 92.8% homologous to its human counterpart, *human* NADE (SEQ ID NO:13) which was previously isolated and named HGR74. No function was known for the HGR74 protein until applicant's discovery of NADE proteins as apoptosis modulators. As disclosed in the specification, NADE, or $P75^{NTR}$-Associated Cell Death Executor, represents a group of proteins, to which HGR74 (human NADE) belongs, that modulate

apoptosis through interaction with the $p75^{NTR}$ receptor. In other words, HGR74 is human NADE. In view of the amendments to the specification and the remarks above, applicant maintains that these minor changes clarify the teachings of the specification and that the specification satisfies the requirements of 37 C.F.R. §1.71(a) and (b).

Rejection under 35 U.S.C. §101

The Examiner rejected claims 134-146 under 35 U.S.C. §101 as allegedly not supported by a specific asserted utility or a well-established utility.

In response, applicant respectfully traverses the Examiner's rejection.

Claims 134-146 provide methods of identifying agents capable of regulating apoptosis. As the Examiner concedes, applicant has shown that NADE interacts with the cell death domain of p75, and has shown that apoptosis only occurs when p75 and NADE are expressed together.

In support of the rejection, the Examiner cites the Bunone et al. reference abstract, which states that "$p75^{NTR}$ could activate the cell death program by itself". The Examiner also asserts that NADE does not appear to be required for regulation of apoptosis, providing no additional utility for the $p75^{NTR}$-NADE complex that $p75^{NTR}$ does not possess alone.

Applicant disagrees with the Examiner's position and maintains that the Bunone et al. statement, by itself, is taken out of

context and does not illustrate the teaching of the Bunone et al. reference. Bunone et al. teach the effect of $p75^{NTR}$ expression in neuroblastoma cells without expression of TrkA. The cited statement in the abstract refers to the findings of Bunone et al. which show that the presence of TrkA is not necessary for $P75^{NTR}$-mediated apoptosis. In other words, the phrase "by itself" means "without TrkA", not "alone" as the Examiner suggests. The authors make it clear on page 1463, second column, second paragraph, that the state of the art at the time of their study was controversial. Some reports indicated the collaboration of $p75^{NTR}$ and TrkA, while others suggested that TrkA or $p75^{NTR}$ may act independently. On page 1468, first column, third paragraph, Bunone et al. confirm that "the survival response to NGF depends on binding of the neurotrophin to $p75^{NTR}$ without any involvement of TrkA or other members of the Trk family." Further, Bunone et al. suggest that other proteins may be involved with the survival response but do not offer any suggestions as to the identity of such proteins. Applicant maintains that the NADE of the instant invention is one of these proteins. Accordingly, applicant maintains that, as described in the specification, apoptosis only occurs when p75 and NADE are expressed together, demonstrating that the NADE-$p75^{NTR}$ complex has a credible utility.

The Examiner further asserts that since NADE alone suppresses NF-kB activity, but not cooperative with expression of $p75^{NTR}$, the NADE-$p75^{NTR}$ complex, on which the claims are based, lacks utility.

Applicant again disagrees with the Examiner's assertion and

directs the Examiner's attention to page 57, line 2-3, which states, in relevant part, that "NF-kB suppression by NADE protein alone could not induce apoptosis" (Emphasis added). Accordingly, applicant maintains that, as stated above, the NADE-$p75^{NTR}$ complex - and hence the claimed methods - have a credible utility.

In view of the above remarks, applicant maintains that claims 134-146 satisfy the requirements of 35 U.S.C. §101.

Rejections under 35 U.S.C. §112, First Paragraph

The Examiner rejected claims 134-146 under 35 U.S.C. §112, first paragraph, as allegedly not enabled by the specification. Specifically, the Examiner maintains that one skilled in the art would not know how to use the claimed invention. The Examiner's rejection is based on the Examiner's assertions set forth in support of the rejection under 35 U.S.C. §101.

In response, applicant respectfully traverses the Examiner's rejection for the reasons set forth above in response to the rejection under 35 U.S.C. §101, and maintains that given the utility of the claimed invention, one would know how to use it.

The Examiner further rejected claims 134-146 under 35 U.S.C. §112, first paragraph, because the specification, while enabling for methods of identifying modulators of apoptosis using NADE and $p75^{NTR}$, allegedly is not enabled for methods using $p75^{NTR}$ and any other cell death executor.

In response, but without conceding the correctness of the Examiner's rejection, applicant regretfully traverses the Examiner's rejection. Applicant notes that, as amended, claims 134-136 and 141-142 provide methods using NADE and $p75^{NTR}$, thereby obviating the rejection.

Furthermore, to address the Examiner's comment on page 5, paragraph 3, of the April 23, 2003 Office Action, applicant notes that, as previously stated, NADE represents a group of proteins capable of binding to the p75 neurotrophin receptor to regulate apoptosis. The instant specification discloses working examples of the interaction between a NADE protein and a p75 neurotrophin receptor. The NADE protein in these examples is the isolated mouse NADE protein (SEQ ID NO:12), but the teaching of these examples extends to other NADE proteins, namely, but not limited to, NADE proteins comprising the amino acid sequence as set forth in SEQ ID NO: 13, as well as SEQ ID NO:30-39.

The Examiner further rejected claims 134-146 under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter that is not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, was in possession of the claimed invention. Specifically, the Examiner asserts that the specification and claims do not indicate what distinguishing attributes are shared by the members of the genus.

In response, applicant respectfully traverses the Examiner's rejection.

Applicant contends that the NADE genus was disclosed in the specification as filed, adequately describing the NADE-specific features and providing numerous embodiments of its species. Applicant directs the Examiner's attention to the subject specification, *inter* alia, at page 16, line 36 to page 17, line 22 and at page 53, lines 21-27, which describe the characteristic attributes of the NADE genus. In relevant part, the specification discloses that NADE proteins are hydrophilic and acidic and possess, in addition to its binding site for the p75 neurotrophin receptor cell death domain (SEQ ID NO:1), two significant motifs: the leucine-rich nuclear export signal (NES) and ubiquitination sequences. In addition, the specification discloses various species of human, mouse and rat NADE, as set forth in SEQ ID NOs:12-13 and SEQ ID NOs:30-39. Accordingly, applicant maintains that the disclosure as filed provides sufficient description of the NADE genus and its role in the regulation of $p75^{NTR}$-mediated apoptosis.

The Examiner further rejected claims 134-146 under 35 U.S.C. §112, first paragraph, because the specification allegedly appears to contain new matter. The Examiner requests that the objection to new matter under 35 U.S.C. §132 as stated by the former Examiner in the March 27, 2002 Office Action be addressed.

Applicant notes that this objection has been addressed by the submission of a substitute sequence listing, in both paper and computer-readable forms, in a November 27, 2002 Amendment In Response To November 1, 2002 Notice To Comply With Requirements For Patent Applications Containing Nucleotide

Sequence And/Or Amino Acid Sequence Disclosures. Accordingly, applicant maintains that the sequence listing as filed in the November 27, 2002 Amendment satisfies the requirements of 37 C.F.R. §1.821-1.825.

In view of the above remarks, applicant maintains that claims 134-146 satisfy the requirements of 35 U.S.C. §112, first paragraph.

Rejection Under 35 U.S.C §112, Second Paragraph

The Examiner rejected claims 134-146 under 35 U.S.C. §112, second paragraph, as allegedly indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, the Examiner asserts that the metes and bounds of the term "NADE" or "cell death executor" is not known.

In response, applicant respectfully traverses the Examiner's rejection.

Applicant notes that, as amended, claims 134-136 and 141-146 provide methods using NADE protein, and do not recite the term "cell death executor". Applicant contends that the language in claims 134-146 particularly points out and distinctly claims the subject invention. As stated above, the specification as filed discloses the metes and bounds of the NADE genus. Again, applicant directs the Examiner's attention to the subject specification, *inter* alia, at page 16, line 36 to page 17, line 22 and at page 53, lines 21-27, which describe the characteristic attributes of the NADE genus. The

specification clearly discloses that NADE proteins bind to the p75 neurotrophin receptor at its cell death domain (SEQ ID NO:1) and possess two other significant motifs, namely NES and ubiquitination sequences. Accordingly, applicant maintains that claims 134-146 particularly point out and distinctly claim methods for identifying apoptosis modulators using NADE proteins.

In view of these remarks, applicant maintains that claims 134-146 satisfy the requirements of 35 U.S.C. §112, second paragraph.

Summary

For the reasons set forth hereinabove, applicant respectfully requests that the Examiner reconsider and withdraw the rejections, and earnestly solicit allowance of the pending claims.

If a telephone interview would be of assistance in advancing prosecution of the subject application, applicant's undersigned attorneys invite the Examiner to telephone them at the number provided below.

No fee is deemed necessary in connection with this Amendment. However, if any fee is required, authorization is hereby given to charge the amount of such fee to Deposit Account No. 03-3125.

Respectfully submitted,

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I hereby certify that this correspondence is being deposited this date with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to:
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P.O. Box 1450 Alexandria, VA 22313-1450.

7/23/03

Alan J. Morrison
Reg. No. 37,399

Date

Abstract of the Disclosure

This invention provides an isolated nucleic acid molecule encoding a polypeptide capable of binding a $p75^{NTR}$ receptor. This invention also provides a method of producing a purified polypeptide capable of binding a $p75^{NTR}$ receptor. This invention further provides an antisense oligonucleotide having a nucleic acid sequence capable of specifically hybridizing to a mRNA molecule encoding the above described polypeptide. This invention further provides a method of producing such polypeptides. Finally, this invention provides a method of inducing apoptosis, a method of determining physiological effects, a method for identifying an apoptosis inducing or inhibiting compound, a method for screening cDNA libraries of the polypeptide, a method to induce caspase-2 and caspase-3 activity, a method to inhibit $NF\text{-}_KB$ activation in a cell, a method to detect a neurodegenerative disease, a pharmaceutical composition comprising the purified polypeptide and a pharmaceutically acceptable carrier and a method of identifying a compound which is an apoptosis inhibitor.

Marked-Up Version of Abstract of the Disclosure

This invention provides an isolated nucleic acid molecule encoding a polypeptide capable of binding a $p75^{NTR}$ receptor[, and a purified version of said polypeptide capable of biding a $p75^{NTR}$ receptor]. This invention also provides a method of producing a purified polypeptide capable of binding a $p75^{NTR}$ receptor. This invention further provides an antisense oligonucleotide having a nucleic acid sequence capable of specifically hybridizing to an mRNA molecule encoding the above described polypeptide. This invention further provides a method of producing [a] such polypeptides [capable of binding a $p75^{NT}$ receptor into a suitable vector]. Finally, this [This] invention provides a method of inducing apoptosis, a method of determining physiological effects, a method for identifying an apoptosis inducing or inhibiting compound, a method for screening cDNA libraries of [said] the polypeptide, a method to induce caspase-2 and caspase-3 activity [to cleave poly (ADP-ribose) polymerase and fragment nuclear DNA in a cell], a method to inhibit $NF\text{-}_{K}B$ activation in a cell, a method to detect a neurodegenerative disease, a method of producing the isolated human HGR74 protein into a suitable vector, a pharmaceutical composition comprising a purified polypeptide capable of binding a $p75^{NTR}$ receptor and a pharmaceutically acceptable carrier and a method of identifying a compound which is an apoptosis inhibitor.

Marked-Up Version of the Specification Paragraphs

Paragraph starting on page 1, line 21, to page 2, line 10:

The low-affinity neurotrophin receptor ($p75^{NTR}$) can mediate cell survival or cell death by NGF or another neurotrophin[s] stimulation in neuronal cells (1, 2, 3). To elucidate $p75^{NTR}$-mediated signal transduction, the yeast two-hybrid system was employed to screen the mouse embryo cDNA libraries using the rat $p75^{NTR}$ICD (intracellular domain) as a target. One positive clone was identified and termed NADE ($p75^{NTR}$-associated cell death executor). This isolated mouse NADE has a significant homology to human HGR74 protein (4) and does not have a typical biochemical motif except the consensus sequences of nuclear export signal (NES) (5) and ubiquitination (6). Expression of NADE mRNA was found highest in the brain, heart, and lung. NADE specifically binds to $p75^{NTR}$ICD both *in vitro and in vivo*. Co-expression of NADE together with $p75^{NTR}$ dramatically induced Caspase-2 and Caspase-3 activities to clave PARP (poly (ADP-ribose) polymerase) and fragmentation of nuclear DNA in 293T cells, but NADE without $p75^{NTR}$ did not show apoptosis suggesting that NADE expression is necessary for $p75^{NTR}$ mediated apoptosis but is not sufficient to trigger apoptosis. Moreover, NGF dependent recruitment of NADE to $p75^{NTR}$ICD was observed in a dose dependent manner and NADE significantly inhibits NF-kB activation. Interestingly, NADE protein is found to be ubiquitinated as a substrate for protein degradation pathway. Taken together, NADE is the first signal adaptor molecule identified in involvement of $p75^{NTR}$-mediated apoptosis, and it may play an important role in the pathogenesis of neurogenetic diseases.

Paragraph starting on page 53, line 20 to line 33:

Mouse NADE consists of 124 amino acids and its molecular weight is calculated to 14,532 dalton. NADE is a hydrophilic and acidic protein, and the estimated p*I* value is 5.97. A BLAST search revealed that mouse NADE has a significant homology to a known human protein HGR74 (4) (Fig. 1a), and does not have a significant motif except the leucine rich nuclear export signal (NES) (5) (Fig. 1b) and ubiquitination sequences (6) (Fig. 1c). HGR74 was previously reported as an abundant mRNA expressed in human ovarian granulosa cells, however, its functional role is still unknown. The homology of these two proteins except the asparagine rich stretch (a. a. 36-48) of mouse NADE is 92.8%, therefore we conclude that HGR74 is a human homolog of mouse NADE.

Marked-Up Version of the Claims:

134. (Amended) A method for determining whether an agent decreases apoptosis comprising:

(a) contacting the agent with a [cell death executor] NADE protein and a p75 neurotrophin receptor under conditions which, in the absence of the agent, permit the formation of a complex between the [cell death executor] NADE protein and the receptor;

(b) determining the amount of complex formed in step (a) between the [cell death executor] NADE protein and the receptor; and

(c) determining whether the amount of complex determined in step (b) is less than the amount of complex formed in the absence of the agent, such lower amount indicating that the agent decreases apoptosis.

135. (Amended) A method for determining whether an agent increases apoptosis comprising:

(a) contacting the agent with a [cell death executor] NADE protein and a p75 neurotrophin receptor under conditions which, in the absence of the agent, permit the formation of a complex between the [cell death executor] NADE protein and the receptor;

(b) determining the amount of complex formed in step (a) between the [cell death executor] NADE protein and the receptor; and

(c) determining whether the amount of complex determined in step (b) is greater than the amount of complex formed in the absence of the agent, such greater amount indicating that the agent increases apoptosis.

136. (Amended) The method of claim 134 or 135, wherein the [cell death executor is] NADE protein comprises the amino acid sequence as set forth in SEQ ID NO:13.

141. (Amended) A method for determining whether an agent decreases apoptosis comprising:

(a) contacting the agent with a cell that expresses a [cell death executor] NADE protein and a p75 neurotrophin receptor;

(b) determining the expression level of the [cell death executor] NADE protein in the cell; and

(c) determining whether the expression level determined in step (b) is lower than the [cell death executor] NADE protein expression level determined in the absence of the agent, such lower expression level indicating that the agent decreases apoptosis.

142. (Amended) A method for determining whether an agent increases apoptosis comprising:

(a) contacting the agent with a cell that expresses a [cell death executor] NADE protein and a p75 neurotrophin receptor;

(b) determining the expression level of the [cell death executor] NADE protein in the

cell; and

(c) determining whether the expression level determined in step (b) is greater than the [cell death executor] NADE protein expression level determined in the absence of the agent, such greater expression level indicating that the agent increases apoptosis.

143. (Amended) The method of claim 141 or 142, wherein the [cell death executor is] NADE protein comprises the amino acid sequence as set forth in SEQ ID NO:13.